# Synthesis and Pharmacological Characterization of a Series of Geometrically Constrained 5-HT$_{2A/2C}$ Receptor Ligands

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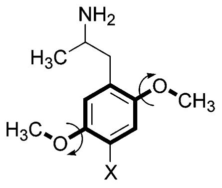
*Received February 11, 2003*

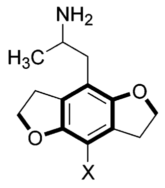
In studies of the SAR of phenethylamine-type serotonin 5-HT$_{2A}$ receptor agonists, substituted conformationally constrained tetrahydronaphthofurans were designed to investigate the optimal conformation of the 2-aminoethyl moiety. These compounds were tested using in vitro assays for affinity at 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{2C}$ receptors. The benzofuran-containing analogues, **6a** and **6b**, had significantly higher affinity for the 5-HT receptors tested than did the benzodihydrofuran-containing compounds, **4a**, **4b**, **5a**, and **5b**. The most potent compound (8-bromo-6-methoxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane, **6b**, had $K_i$ values for displacement of [$^{125}$I]-DOI from 5-HT$_{2A}$ and 5-HT$_{2C}$ cloned rat receptors of 2.6 and 1.1 nM, respectively. Despite their high affinity, the compounds of this naphthofuran series lacked high intrinsic activity at the 5-HT$_{2A}$ receptor as measured using the phosphoinositide hydrolysis assay. The most potent compound in vitro, **6b**, was tested in the two-lever drug discrimination assay in rats trained to discriminate LSD from saline, and failed to substitute, a result typical for compounds with low intrinsic activity. Thus, although conformational constraint has led to high-affinity 5-HT$_{2A}$ ligands with partial agonist activity, all of the spatial and steric properties of the ligand necessary for full receptor activation have not yet been identified.

## Introduction

Conformational restriction of bioactive molecules is a valuable tool for investigating the topographical and chemical features of small-molecule binding sites. Restraint of flexible molecules into distinct conformations often allows one to test the functional effects of a subset of the total conformational space. Recently, for example, we have discovered by use of a conformational-restriction design method the optimal orientation for the 2,5-dimethoxy groups of typical hallucinogenic arylalkylamines (**1**, DOM, X = $CH_3$; DOB, X = Br; DOTFM, X = $CH_3$).[1−3] The optimal conformations parallel those where the methyl groups are tethered to the phenyl ring in the form of dihydrofuran rings as in compound **2**.

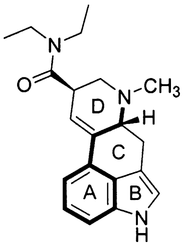



**1**

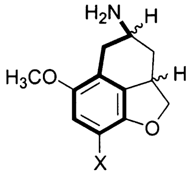



**2**

Further investigation of arylalkylamines in our laboratory by the use of conformational restriction has recently focused on the 2-aminoalkyl side chain.[4] Conformationally restricted analogues of arylalkylamines in which the 2-aminoalkyl side chain has been constrained by incorporation into a tethered ring system have most recently focused on a series of 4-aminotetrahydronaphthofurans.[4] The compounds of this series were considered to be "hybrid" structures of the hallucinogenic arylalkylamine and ergoline families because it had been hypothesized since the late 1950s that the A ring of LSD corresponds to the phenyl ring of the arylalkylamines and that the 5-oxygen of arylalkylamines serves as a bioisostere of the indole N-1 nitrogen of LSD. Thus, tetrahydronaphthofuran series **3** was hypothesized to mimic the A, B, and C rings of LSD.




LSD




**3**; X = H, Br

The majority of the compounds in series **3**, however, exhibited rather low affinity for the 5-HT$_{2A}$ receptor, and none of those compounds produced LSD-like effects in a drug discrimination animal model believed to reflect the subjective behavioral effects of hallucinogenic drugs. One compound of series **3**, the brominated syn analogue, did, however, possess high affinity for the 5-HT$_{2A}$ receptor but lacked an LSD-like behavioral effect in animals.[4] These results suggested that the hypothesized structural correlation between the arylalkylamine and ergoline families was incorrect. The high binding affinity but lack of hallucinogen-like behavioral activity of the syn brominated analogue of series **3** indicated that this

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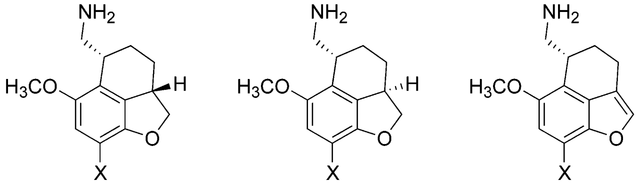
10.1021/jm030064v CCC: $25.00 © 2003 American Chemical Society
Published on Web 07/04/2003

drug might be an antagonist and lack the ability to activate the receptor.

We, therefore, abandoned the notion of structural similarity between ergolines and phenethylamines and considered a de novo approach. Specifically, new tetrahydronaphthofurans, compounds **4**−**6**, were designed on the basis of a molecular scaffold similar to that of series **3** to alter the spatial orientation of the aminoethyl moiety in the ligand. The compounds in the new series



**4a**; X = H  **5a**; X = H  **6a**; X = H
**4b**; X = Br  **5b**; X = Br  **6b**; X = Br

were designed also to exploit knowledge we had gained about the active orientation of the 2- and 5-alkoxy substituents of arylalkylamines. Most importantly, we decided to examine conformations of the aminoethyl moiety that were distinctly out of the aromatic ring plane (i.e., nonplanar).

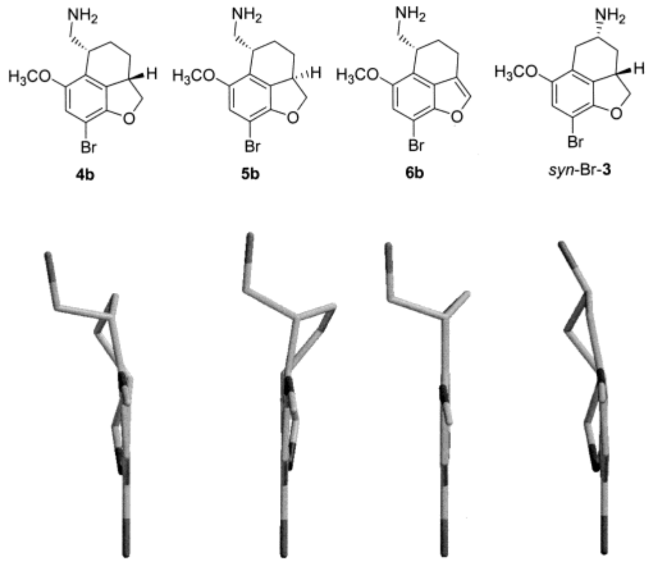
The alkoxy substituent of compounds **4**−**6** that corresponds to the 5-methoxy group of typical arylalkylamines is incorporated into an appended dihydrofuran ring. The peri interaction between the 6-methoxy group and the buttressing by the adjacent methylene forces the aminomethyl to adopt a conformation that we hypothesized might be near optimal. Thus, compounds **4**−**6** localize the basic amine moiety to a region of space that is out of the plane defined by the phenyl ring. Conformational restriction of the alkylamine was designed to test the hypothesis that the 2-aminoalkyl side chain of arylalkylamines adopts an anti-periplanar conformation upon binding to the 5-HT$_{2A}$ receptor agonist binding site. The hypothesis that the amine must lie in an anti-periplanar conformation and out of the plane of the phenyl ring is based, in part, on solution NMR studies of amphetamine.[5]

Molecular modeling of compounds **4b**, **5b**, and **6b** and the compound that exhibited the highest 5-HT$_{2A}$ receptor affinity of series **3**, the syn brominated analogue, revealed that compounds **4b**, **5b**, and **6b** adopt an energetically favored conformation that resembles closely an anti-periplanar conformation (Figure 1). The three compounds **4b**, **5b**, and **6b** all position the basic amine out of the plane of the phenyl ring (semiempirical generated models using Spartan[6] and AM-1 potentials). Although syn brominated **3** can mimic an anti-periplanar conformation as well, the basic amine is locked into a position closer to the plane of the phenyl ring than the compounds of the presently described series.

In addition to investigation of the optimal 2-aminoalkyl conformation, compounds **4**−**6** were designed to probe the effect of aromatization of the dihydrofuran ring. It was predicted, on the basis of previous work,[2,3] that aromatization of the dihydrofuran ring would increase the affinity and efficacy of these compounds at the 5-HT$_{2A}$ receptor.

## Chemistry

Retrosynthetic analysis of the target naphthofurans **4**−**6** revealed that all six racemic compounds of the




**4b** **5b** **6b** **syn-Br-3**

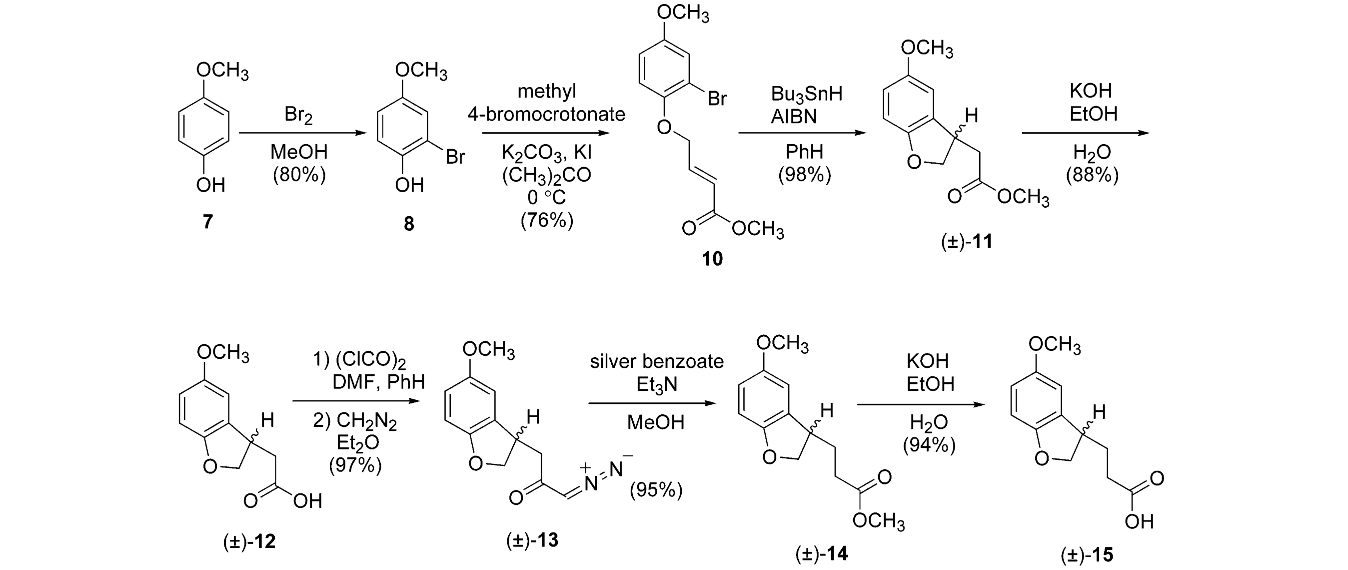
**Figure 1.** Illustration of out-of-plane, anti-periplanar conformation for compounds **4b**, **5b**, and **6b** compared to in-plane, anti-periplanar naphthofuran *syn*-Br-**3** as viewed from the 6,7-edge of the molecule. The amino group is at the uppermost top of each structure, with the bromine atom at the very bottom. Hydrogen atoms have been omitted for clarity.

proposed series could be derived from a single intermediate, (±)-**4a**, also one of the target compounds. The nonaromatized compounds of this naphthofuran series contain two stereocenters and thus two pairs of enantiomers, the syn and anti racemates. A divergent synthetic scheme was designed to generate separately each enantiomeric pair. Various combinations of bromination, N-protection/deprotection, aromatization, and reduction of (±)-**4a** were envisioned to generate the remainder of the series from this divergent intermediate.

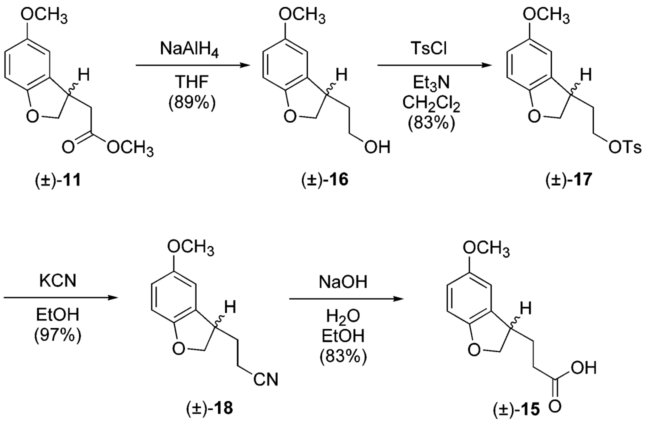
Synthesis of compounds (±)-**4**, (±)-**5**, and (±)-**6** (Scheme 1) commenced with the regioselective bromination of 4-methoxyphenol (**7**) to afford **8** utilizing a method described by Curran et al.[7] Substituted phenol **8** was subsequently O-alkylated using Finkelstein conditions with methyl 4-bromocrotonate (**9**) to yield **10**. Utilization of exactly 1 equiv of potassium carbonate and a reaction temperature of 0 °C resolved difficulties associated with the synthesis of this $\gamma$-aryloxycrotonate.[8] The methyl ester **10** was then subjected to radical reaction conditions to effect ring closure and afford benzofuran (±)-**11**.[9] Limitations imposed by the high-dilution requirements of typical radical reactions were overcome by employing a reaction design that maintained a low concentration of tributyltin hydride, thus resulting in fewer side reactions. Benzofuran (±)-**11** was then subjected to base hydrolysis to afford substituted acetic acid (±)-**12**.[4] Next, (±)-**12** was converted to the acyl chloride with oxalyl chloride and subsequently to diazoketone (±)-**13** by reaction with diazomethane.[4] Diazoketone (±)-**13** was then subjected to Wolff rearrangement by treatment with silver benzoate and triethylamine in methanol to afford the homologated methyl ester (±)-**14**.[10] Ester (±)-**14** was subsequently hydrolyzed with base to afford propionic acid (±)-**15**.

An alternative approach (Scheme 2) was also em-

**Scheme 1**




**Scheme 2**



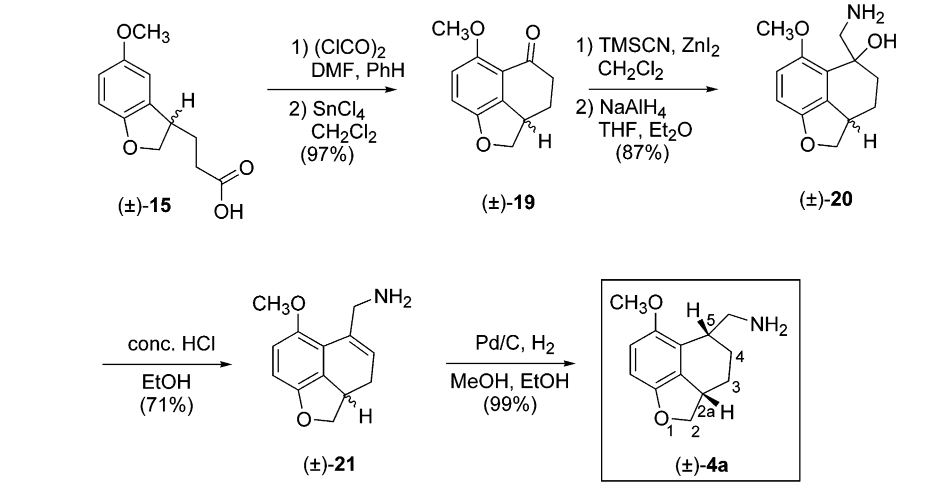

ployed to generate a larger quantity of propionic acid (±)-**15**. This synthetic route involved reduction of methyl ester (±)-**11** to alcohol (±)-**16** using sodium aluminum hydride, followed by protection of the alcohol to afford tosylate (±)-**17**.[11] The tosylate group was then displaced by reaction with potassium cyanide in ethanol to afford (±)-**18**, followed by base hydrolysis of the nitrile to generate homologated acid (±)-**15**.

Propionic acid (±)-**15** was then converted to the acyl chloride and subjected to Friedel–Crafts conditions to effect ring closure and afford tricyclic ketone (±)-**19** (Scheme 3).[12,13] The ketone moiety of (±)-**19** was functionalized utilizing reaction with trimethylsilyl cyanide and zinc iodide in dichloromethane.[14,15] The adduct that was formed by this reaction could not be purified and was reduced directly with sodium aluminum hydride to afford amino alcohol (±)-**20**. This alcohol was then dehydrated using acidic conditions to yield substituted aminomethylstyrene (±)-**21**. Subsequently, catalytic reduction of (±)-**21** to afford exclusively syn product (±)-**4a** was accomplished. It was anticipated that reduction of styrene (±)-**21** would result in a mixture of syn and anti products (±)-**4a** and (±)-**5a** that would be amenable to separation by chromatography. Interestingly, however, $^1$H NMR examination of the product of this reaction indicated the absence of the anti epimer. X-ray analysis of hydrochloride salt crystals of compound (±)-**4a** confirmed the syn geometry of the product. It is hypothesized that the selectivity observed in the catalytic reduction of (±)-**21** arose from steric-induced facial selectivity. The occurrence of facial selectivity in compounds that have structures similar to styrene (±)-**21** has been observed and reported in the literature.[16,17]

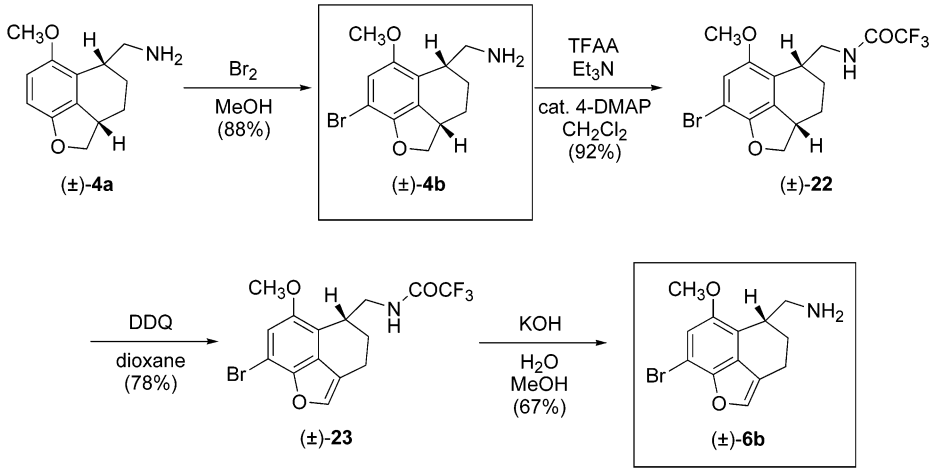
Synthesis of the remaining target compounds of the current naphthofuran series began with aromatic bromination of (±)-**4a** to afford the syn brominated product (±)-**4b** (Scheme 4). Next, a sample of (±)-**4b** was N-protected to afford (±)-**22**. Selective oxidation of the dihydrofuran ring of (±)-**22** was accomplished utilizing reaction with exactly 1 equiv of DDQ in dioxane to afford (±)-**23**. Base hydrolysis was then employed to remove the N-protecting group and liberate the product (±)-**6b**.

Finally, a portion of (±)-**4a** was N-protected as the trifluoroacetamide to afford (±)-**24** (Scheme 5). Trifluoroacetamide (±)-**24** was subsequently oxidized utilizing reaction with 1 equiv of DDQ to afford (±)-**25**. The N-protecting group of (±)-**25** was then removed by base hydrolysis to afford (±)-**6a**. A further review of literature pertaining to facially selective hydrogenation suggested that the two target anti products, (±)-**5a** and (±)-**5b**, of the current series could be obtained by utilizing conditions that favor catalyst coordination with the primary amine of the substrate molecule.[18–20] It was anticipated that metal-mediated reduction in a nonpolar solvent would enable the basic amine moiety of (±)-**6a** to interact electronically with the metal catalyst, and thus, hydrogen delivery from the metal would occur on the same face as the amino group, resulting in the anti product (±)-**5a**.[20] Indeed, catalytic hydrogenation of primary amine (±)-**6a** in hexane proceeded as anticipated and $^1$H NMR studies of the crude product indicated that the reduction had produced an approximately 97:3 ratio of anti/syn isomers. The $^1$H NMR spectra of (±)-**4a** and (±)-**5a** are dissimilar in the spectral region that corresponds to aliphatic protons. The benzylic protons (of C-2a and C-5) of (±)-**4a** appear in the spectrum as two distinct groups of peaks at approximately 2.9 and 3.2 ppm, whereas the corresponding protons of (±)-**5a** are found as a multiplet at approximately 3.4 ppm. There are also significant splitting

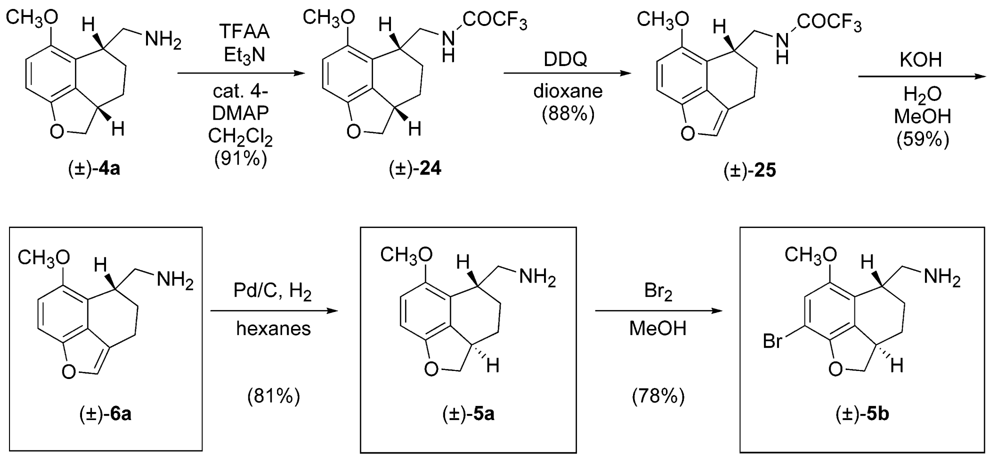
**Scheme 3**




**Scheme 4**




**Scheme 5**




pattern and frequency differences for the methylene protons (of C-3 and C-4) of the two products. A sample of (±)-**5a** was then brominated using bromine in methanol to afford anti product (±)-**5b**. The anti geometries of compounds (±)-**5a** and (±)-**5b** were ultimately confirmed by X-ray analysis of a crystal of the tosylate salt of (±)-**5b**.

## Discussion

Compounds (±)-**4** - (±)-**6** were assayed for their ability to bind to the 5-HT$_{2A}$ receptor and to activate the phospholipase C pathway by quantification of IP$_3$ accumulation. The receptor affinity results (Table 1) show that the three brominated compounds, (±)-**4b**, (±)-**5b**, and (±)-**6b**, possess nanomolar affinity for the receptor. The analogues lacking the bromine, (±)-**4a**, (±)-**5a**, and (±)-**6a**, had significantly lower affinity for the 5-HT$_{2A}$ receptor. Direct comparison of brominated and non-brominated counterparts (e.g., (±)-**4b** vs (±)-**4a**, (±)-**5b** vs (±)-**5a**, and (±)-**6b** vs (±)-**6a**) shows that the presence of a bromine atom on the phenyl ring results in a 33- to

**Table 1.** Results of Radioligand Competition Binding Studies at Cloned Receptors

| | $K_i$ (SEM), nM | | |
|---|---|---|---|
| compd | 5-$HT_{2A}$ (±)-[$^{125}$I]-DOI | 5-$HT_{2C}$ (±)-[$^{125}$I]-DOI | 5-$HT_{1A}$ [$^{3}$H]-8-OH-DPAT |
| (±)-*syn*-Br-**3** | 16(1.5) | 4.0(0.2) | 960(48) |
| (±)-**4a** | 700(130) | 59(0.6) | 3000(460) |
| (±)-**4b** | 8.7(0.2) | 2.8(0.2) | 520(67) |
| (±)-**5a** | 310(34) | 34(4.7) | 1000(336) |
| (±)-**5b** | 9.3(0.2) | 4.9(0.6) | 550(81) |
| (±)-**6a** | 200(9.2) | 11(1.2) | 860(170) |
| (±)-**6b** | 2.6(0.2) | 1.1(0.2) | 105(6) |
| DOB | 2.2(0.3)[a] | 2.8(0.7)[a] | nd[b] |
| psilocin | 25(4.7) | nd[b] | nd[b] |
| LSD | 3.5(0.62) | 5.5(0.31) | 1.1(0.01) |

[a] Data from Chambers et al.[3] [b] nd = not determined.

**Table 2.** Results of $IP_3$ Accumulation Studies at Cloned Rat 5-$HT_{2A}$ Receptors

| compd | $EC_{50}$ (SEM) at 5-$HT_{2A}$, nM | % max 5-HT stimulation (SEM) |
|---|---|---|
| (±)-*syn*-Br-**3** | 2090(125) | 63(3.0) |
| (±)-**4a** | nd[a] | nd[a] |
| (±)-**4b** | 1100(283) | 49(8.0) |
| (±)-**5a** | nd[a] | nd[a] |
| (±)-**5b** | 340(65) | 37(8.0) |
| (±)-**6a** | >10000 | 10 @ 10 μM |
| (±)-**6b** | 120(14) | 33(2.0) |
| DOB | 72(3.6) | 79(6.0) |
| psilocin | 2300(290) | 46(2.4) |
| mescaline | 2600(360) | 92(6.3) |
| LSD | 9.8(3.7) | 22(2.6) |

[a] nd = not determined.

**Table 3.** Results of Drug Discrimination Studies in LSD- or DOI-Trained Rats

| | LSD-trained | | DOI-trained | |
|---|---|---|---|---|
| compd | $ED_{50}$, μmol/kg | 95% CI | $ED_{50}$, μmol/kg | 95% CI |
| (±)-**6b**[a] | PS[b] (25−67%) | | PS[b] (43−75%) | |
| DOB | 1.06 | (0.82−1.36) | 0.091 | (0.0049−0.017) |

[a] **6b** was tested at doses from 1 to 6 μmol/kg (0.36−2.2 mg/kg). [b] PS = partial substitution.

81-fold increase in affinity for members of this series. A general requirement for potent hallucinogenic arylalkylamines is that the substituent at the para position, the 8-position of the currently discussed series, be a bulky, hydrophobic group.[21−23] If one assumes that these new analogues are binding to the receptor in the same general orientation as the simpler phenethylamine congeners such as **1** or **2**, then the disparity in affinity between brominated and non-brominated compounds in this series is not surprising. Indeed, one could use the fact that the bromine dramatically enhances affinity to argue that these new rigid analogues are binding in the same region of the receptor as the prototype flexible phenethylamines.

The benzofuran-containing compounds (±)-**6a** and (±)-**6b** exhibited significantly higher affinity for the 5-$HT_{2A}$ receptor than their corresponding nonaromatized counterparts. Again, this result was not surprising in light of our previous findings that extension of the core aromatic system to the dihydrofuran rings of compounds containing the tetrahydrobenzo[1,2-*b*;4,5-*b*′]-difuran nucleus enhances affinity and efficacy at this receptor.[2,3] Although it is not clear how this effect occurs, oxidation of the dihydrofuran ring increases the aromatic surface area of the drug, perhaps aiding lipophilic partitioning into, and enhancement of hydrophobic interactions within, the agonist binding site.

Finally, a comparison of 5-$HT_{2A}$ receptor affinity shows that there is little difference between the pair of syn and the pair of anti compounds. These results indicate no appreciable difference between the brominated syn product (±)-**4b** compared to anti product (±)-**5b** and only about a 2-fold difference between the non-brominated syn (±)-**4a** and anti (±)-**5a**; it appears that both syn and anti compounds may be accommodated about equally well within the binding site. This similarity may be explained by the observation that the syn and anti compounds differ only slightly in their respective three-dimensional molecular structure. Comparison of syn (±)-**4b** and anti (±)-**5b** illustrates the apparently minor difference between them (Figure 1). Further, when these structures are docked into a recently developed homology model of the 5-$HT_{2A}$ receptor,[24] the bulk of the reduced carbocyclic ring projects toward the extracellular surface of the receptor into a region that would appear to have considerable bulk tolerance. Thus, the difference with respect to binding to the agonist site of the 5-$HT_{2A}$ receptor could also be construed as being minor and may explain their similar pharmacology. The aromatic compound (±)-**6b** is likewise very similar in molecular shape to the respective syn and anti (±)-**4b** and (±)-**5b**. This latter observation suggests that the increase in binding affinity that results from aromatization of the dihydrofuran ring may be largely of an electronic or hydrophobic nature.

Compounds (±)-**4b**, (±)-**5b**, (±)-**6a**, and (±)-**6b** were tested for their ability to activate the phospholipase C pathway by quantification of $IP_3$ accumulation. These data (Table 2) indicate that the compounds tested are only partial agonists in this functional assay. The most potent of the new compounds, (±)-**6b**, while possessing a submicromolar $EC_{50}$, also was only a weak partial agonist. The brominated compounds of the novel present series, (±)-**4b**, (±)-**5b**, and (±)-**6b**, however, displayed at least 2-fold increased functional potency compared to the previously synthesized syn brominated (±)-**3**. It is apparent that the addition of the bromine substituent also increases functional potency, another attribute that parallels results seen in more flexible compounds such as **1** and **2**. In some cases, this effect is very robust, where the $EC_{50}$ values of (±)-**6a** and (±)-**6b** differ by about 100-fold. Once again, this finding could be interpreted to mean that these new analogues are binding in the same region of the receptor as the more flexible prototype compounds.

Finally, we selected the compound that was found to be the most potent during in vitro analysis ((±)-**6b**) for behavioral tests in the two-lever drug discrimination assay in rats trained to discriminate either saline from LSD or saline from the hallucinogenic amphetamine DOI (Table 3). Compound (±)-**6b** in this paradigm displayed, however, only partial substitution at the highest dose tested. Despite its high affinity for the 5$HT_{2A}$ receptor, (±)-**6b** did not engender LSD-like responding. Although in DOI-trained rats **6b** elicited 75% drug lever selection at the highest dose tested (6 μmol/kg), our criterion for full substitution is >80% drug lever selection. The lack of LSD-like in vivo activity is not related to pharmacokinetic factors because rats did

emit behavioral responses (25−43% drug lever selection) even at the lowest dose tested (1 $\mu$mol/kg). We have previously reported on a series of mescaline analogues in which LSD-like activity appeared to depend on intrinsic activity in the PLC signaling pathway.[25] With an intrinsic activity of only 33% that of serotonin, (±)-**6b** may simply fail to provide sufficient activation of the receptor. The partial agonist character of **4b**, **5b**, and **6b** was also evident when 1−10 $\mu$M concentrations were incubated with the 5-HT$_{2A}$ cells in the presence of 10 $\mu$M 5-HT and the IP$_3$ response was inhibited from 25% to 35% (data not shown). The lack of in vivo LSD-like activity thus indicates that the novel compounds reported here would not possess hallucinogenic activity in man.

We are presently investigating several new areas as a result of these findings. First, although rigid analogue design can be very imprecise, on the basis of the effect of the bromine atom substitution in the present series, we hypothesize that the compounds are binding in the relevant region of the receptor. The lack of LSD-like activity leads to at least three hypotheses: (1) that the tethering bulk cannot be tolerated by the receptor, (2) that the "side chain" is not fixed into an appropriate dihedral angle for helical movement in the receptor that would lead to activation, and (3) that the side chain may require more conformational freedom for receptor activation to occur. The argument against the last hypothesis, however, is that LSD, a very rigid molecule, is active. We are currently pursuing the second explanation, with the construction of additional constrained analogues.

## Experimental Section

**Chemistry.** All reagents were commercially available and were used without further purification unless otherwise indicated. Anhydrous THF was obtained by distillation from benzophenone-sodium under nitrogen immediately before use. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. $^1$H NMR spectra were recorded using either a 500 MHz Varian DRX-5000s or a 300 MHz Bruker ARX-300 NMR spectrometer. Chemical shifts are reported in $\delta$ values (ppm) relative to an internal reference (0.03%, v/v) of tetramethylsilane (TMS) in $CDCl_3$, except where noted. Chemical ionization mass spectra (CIMS), using isobutane as the carrier gas, were obtained with a Finnigan 4000 spectrometer. Elemental analyses were performed by the Purdue University Microanalysis Laboratory and are within ±0.4% of the calculated values unless otherwise noted. Thin-layer chromatography was performed using J. T. Baker flex silica gel IB2-F, plastic-backed sheets with fluorescent indicator, visualizing with UV light at 254 nm and with the product eluting with 4:1 hexanes/ethyl acetate unless otherwise noted. Column chromatography was carried out using silica gel 60, 230−400 mesh (J. T. Baker). All reactions were carried out under an inert atmosphere of argon unless otherwise indicated.

**2-Bromo-4-methoxyphenol (8).**[7] Bromine (285 g, 1.78 mol) was added dropwise to a stirred solution of 4-methoxyphenol (**7**) (200 g, 1.61 mol) in MeOH (840 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed by rotary evaporation and the residue was purified by vacuum distillation (130 °C at 25 mmHg) to afford a clear liquid (262 g, 80%); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.72 (s, 3 H, OC$H_3$), 5.18 (bs, 1 H, O$H$), 6.78 (dd, 1 H, Ar$H$, $J$ = 8.9, 3.0 Hz), 6.92 (d, 1 H, Ar$H$, $J$ = 8.9 Hz), 7.00 (d, 1 H, Ar$H$, $J$ = 3.0 Hz); MS (CI) $m/z$ 203 (M + H).

**Methyl 4-(2-Bromo-4-methoxyphenoxy)but-2-enoate (10).** To a mechanically stirred solution of **8** (193 g, 950 mmol) in anhydrous acetone (1.0 L) was added potassium carbonate (131 g, 950 mmol) and potassium iodide (159 g, 958 mmol). This mixture was stirred and cooled to 0 °C followed by dropwise addition over 2 h of methyl 4-bromocrotonate (170 g, 951 mmol) in anhydrous acetone (1.5 L). The reaction mixture was allowed to warm to room temperature and was stirred for 18 h. $Et_2O$ (500 mL) was added, and the mixture was then vacuum-filtered. The filter cake was washed well with acetone (500 mL), and the filtrate was evaporated. The resulting residue was dissolved in $Et_2O$ (700 mL) and washed with cold, aqueous 2 N NaOH (2 × 200 mL). The organic layer was washed with brine (200 mL), dried ($MgSO_4$), filtered, and evaporated to leave a light-yellow oil that solidified upon cooling. This solid was recrystallized from $Et_2O$ to afford large, tan crystals (229 g, 76%): mp 48−49 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.73 (s, 3 H, ArOC$H_3$), 3.74 (s, 3 H, $CO_2CH_3$), 4.66 (q, 2 H, ArOC$H_2$, $J$ = 2.1 Hz), 6.27 (dt, 1 H, ArOCH$_2$CHC$H$, $J$ = 15.6, 2.1 Hz), 6.77 (m, 2 H, Ar$H$), 7.02 (dt, 1 H, ArOCH$_2$C$H$CH, $J$ = 15.9, 3.6 Hz), 7.09 (m, 1 H, Ar$H$); MS (CI) $m/z$ 301 (M + H), Anal. ($C_{12}H_{13}BrO_4$) C, H.

**(±)-Methyl 2-(2,3-Dihydro-5-methoxybenzofuran-3-yl)-acetate ((±)-11).** To a stirred solution of compound **10** (32.8 g, 109 mmol) in anhydrous benzene (1140 mL) at reflux was added portionwise AIBN (1.6 g, 10 mmol). To this mixture was added $Bu_3SnH$ (32.3 mL, 120 mmol) dissolved in anhydrous benzene (420 mL) dropwise over a period of 1.5 h. The reaction mixture was maintained at reflux for an additional 1 h and was then cooled to room temperature. The solvent was removed by rotary evaporation, the resulting residue was dissolved in $Et_2O$ (1.0 L), and an aqueous solution of potassium fluoride (60% w/v, 150 mL) was added. This mixture was stirred vigorously overnight. The precipitate that formed was removed by vacuum filtration, and the filter cake was washed well with $Et_2O$ (500 mL). The filtrate was evaporated and subjected to flash chromatography (4:1 hexanes/EtOAc). Fractions containing the product were pooled and the solvent was removed by rotary evaporation to leave a clear oil (24 g, 98%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.54 (dd, 1 H, C$H_2$CO$_2$CH$_3$, $J$ = 16.8, 9.0 Hz), 2.74 (dd, 1 H, C$H_2$CO$_2$CH$_3$, $J$ = 16.8, 5.7 Hz), 3.68 (s, 3 H, CO$_2$C$H_3$), 3.71 (s, 3 H, ArOC$H_3$), 3.80 (m, 1 H, ArC$H$, $J$ = 2.7 Hz), 4.18 (dd, 1 H, ArOC$H_2$, $J$ = 9.0 Hz), 4.68 (t, 1 H, ArOC$H_2$, $J$ = 9.0 Hz), 6.68 (m, 3 H, Ar$H$); MS (CI) $m/z$ 223 (M + H). Anal. ($C_{12}H_{14}O_4$) C, H.

**(±)-(2,3-Dihydro-5-methoxybenzofuran-3-yl)acetic Acid (±)-12).** A solution of $H_2O$ (100 mL), EtOH (50 mL), and KOH (20.0 g, 357 mmol) was added to a solution of methyl ester (±)-**11** (11.9 g, 53.6 mmol) in EtOH (100 mL). This mixture was heated at reflux for 1 h and then cooled to room temperature. The solvents were removed by rotary evaporation, and the resulting residue was dissolved in $H_2O$ (50 mL) and acidified with cold, concentrated HCl. This solution was then extracted with $CH_2Cl_2$ (4 × 40 mL), and the organic layers were pooled and washed with brine, dried ($MgSO_4$), filtered, and evaporated to leave a white solid. The product was recrystallized from EtOAc to yield white, granular crystals (9.8 g, 88%): mp 110−112 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 2.54 (dd, 1 H, C$H_2$CO$_2$H, $J$ = 14.0, 9.5 Hz), 2.82 (dd, 1 H, C$H_2$-CO$_2$H, $J$ = 14.3, 5.6 Hz), 3.72 (s, 3 H, ArOC$H_3$), 3.75 (m, 1 H, ArC$H$, $J$ = 6.5 Hz), 4.17 (dd, 1 H, ArOC$H_2$, $J$ = 8.8, 7.1 Hz), 4.69 (t, 1 H, ArOC$H_2$, $J$ = 8.9 Hz), 6.67 (s, 2 H, Ar$H$), 6.91 (s, 1 H, Ar$H$), 12.40 (bs, 1 H, CO$_2$$H$); MS (CI) $m/z$ 209 (M + H). Anal. ($C_{11}H_{12}O_4$) C, H.

**(±)-1-Diazo-3-(2,3-dihydro-5-methoxybenzofuran-3-yl)-propan-2-one ((±)-13).**[4] To a solution of acid (±)-**12** (5.0 g, 24.0 mmol) in anhydrous benzene (40 mL) was added DMF (2 drops) followed by the dropwise addition of oxalyl chloride (2.72 mL, 31.2 mmol). After the mixture was stirred for 3 h, the solvent and excess oxalyl chloride were removed by rotary evaporation. Meanwhile, an $Et_2O$ solution of $CH_2N_2$ cooled in an ice/salt bath was generated using an Aldrich Diazald Kit and a Diazald (16.47 g, 76.9 mmol) solution in $Et_2O$ (105 mL) dripped into a 60 °C solution of KOH (5.25 g, 94 mmol) in Carbitol (32 mL) and $H_2O$ (11 mL). The solid acyl chloride of (±)-**12** was dissolved in anhydrous $Et_2O$ (55 mL) and added dropwise to the $CH_2N_2$ solution. After the mixture was stirred at 0 °C for 1.5 h, a precipitate formed and the excess $CH_2N_2$

was removed by attaching the apparatus to a water aspirator. After most of the solvent had been removed, the remaining volatiles were removed by rotary evaporation to leave the diazoketone as a yellow solid (5.4 g, 97%). An analytical sample of the diazoketone was recrystallized from $Et_2O$: mp 70−72 °C (lit.[4] mp 73−74 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.74 (m, 2 H, $CH_2COCHN_2$), 3.74 (s, 3 H, $ArOCH_3$), 3.90 (m, 1 H, ArC*H*), 4.19 (dd, 1 H, $ArOCH_2$, $J$ = 9.1, 6.0 Hz), 4.70 (t, 1 H, $ArOCH_2$, $J$ = 9.0 Hz), 5.25 (s, 1 H, $CH_2COCHN_2$), 6.73 (m, 3 H, Ar*H*); MS (CI) *m*/*z* 233 (M + H).

**(±)-Methyl 3-(2,3-Dihydro-5-methoxybenzofuran-3-yl)-propionate ((±)-14).** To a stirred solution of diazoketone (±)-**13** (5.4 g, 23.3 mmol) in anhydrous MeOH (100 mL) was added *very slowly* a solution of silver benzoate (0.4 g, 1.7 mmol) in anhydrous $Et_3N$ (4.0 mL). This reaction mixture was stirred overnight and was then diluted with $Et_2O$ (100 mL) and vacuum-filtered to remove the solids. The filter cake was washed well with $Et_2O$, and the filtrate was concentrated. The residue was dissolved in $CH_2Cl_2$ (200 mL), washed with aqueous 0.5 M NaOH (2 × 40 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and evaporated to leave a tan oil (5.2 g, 95%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.93 (m, 1 H, $ArCHCH_2CH_2$), 2.08 (m, 1 H, $ArCHCH_2CH_2$), 2.38 (m, 2 H, $ArCHCH_2CH_2$), 3.42 (m, 1 H, ArC*H*), 3.67 (s, 3 H, $CO_2CH_3$), 3.77 (s, 3 H, $ArOCH_3$), 4.19 (dd, 1 H, $ArCHCH_2O$, $J$ = 8.8, 5.8 Hz), 4.59 (t, 1 H, $ArCHCH_2O$, $J$ = 8.8 Hz), 6.68 (m, 2 H, Ar*H*), 6.75 (s, 1 H, Ar*H*); MS (CI) *m*/*z* 237 (M + H). Anal. ($C_{13}H_{16}O_4$) C, H.

**(±)-3-(2,3-Dihydro-5-methoxybenzofuran-3-yl)propionic Acid ((±)-15).** Methyl ester (±)-**14** (5.2 g, 22.0 mmol) was dissolved in EtOH (80 mL), a solution of KOH (5.0 g, 89.0 mmol) in $H_2O$ (25 mL) and EtOH (13 mL) was added, and the mixture was stirred overnight. The EtOH was removed by rotary evaporation, and the resulting mixture was diluted with $H_2O$ (50 mL) and acidified with cold, concentrated HCl. The resulting suspension was extracted with $CH_2Cl_2$ (4 × 40 mL), and the organic layers were pooled, washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to leave a white, amorphous solid. This solid was recrystallized from $Et_2O$ to afford white crystals (4.6 g, 94%): mp 100−101 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.77 (m, 1 H, $ArCHCH_2CH_2$), 2.00 (m, 1 H, $ArCHCH_2CH_2$), 2.34 (m, 2 H, $ArCHCH_2CH_2$), 3.48 (m, 1 H, ArC*H*), 3.73 (s, 3 H, $ArOCH_3$), 4.22 (dd, 1 H, $ArCHCH_2O$, $J$ = 8.7, 6.0 Hz), 4.59 (t, 1 H, $ArCHCH_2O$, $J$ = 9.5 Hz), 6.72 (m, 2 H, Ar*H*), 6.91 (s, 1 H, Ar*H*), 12.21 (bs, 1 H, $CO_2H$); MS (CI) *m*/*z* 223 (M + H). Anal. ($C_{12}H_{14}O_4$) C, H.

**Alternative Route to Propionic Acid (±)-15. (±)-2-(5-Methoxy-2,3-dihydrobenzofuran-3-yl)ethanol ((±)-16).** To a stirred suspension of lithium aluminum hydride (32.0 g, 840 mmol) in anhydrous $Et_2O$ (500 mL) was added dropwise an anhydrous $Et_2O$ (450 mL) solution of methyl ester (±)-**11** (45.5 g, 205 mmol). The reaction mixture was stirred at room temperature overnight and quenched by the *careful dropwise* addition of a solution of $H_2O$ (25 mL) in THF (250 mL) followed by 5 N KOH (20 mL). The solids were removed by vacuum filtration through a pad of Celite, and the filter cake was washed well with warm THF (500 mL). The solvents were then removed by rotary evaporation to leave a clear oil that was homogeneous by TLC analysis (39.0 g, 89%). An analytical sample was purified by column chromatography (1:1 hexanes/EtOAc as eluent): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.61 (bs, 1 H, $CH_2OH$), 1.84 (m, 1 H, $ArCHCH_2CH_2$), 2.04 (m, 1 H, $ArCHCH_2CH_2$), 3.56 (m, 1 H, ArC*H*), 3.75 (t, 2 H, $ArCHCH_2CH_2$, $J$ = 4.2 Hz), 3.76 (s, 3 H, $ArOCH_3$), 4.25 (dd, 1 H, $ArCHCH_2O$, $J$ = 8.9, 6.5 Hz), 4.65 (t, 1 H, $ArCHCH_2O$, $J$ = 8.9 Hz), 6.68 (m, 2 H, Ar*H*), 6.77 (m, 1 H, Ar*H*); MS (CI) *m*/*z* 195 (M + H), 177 (M + H − $H_2O$). Anal. ($C_{11}H_{14}O_3$) C, H.

**Continuation of Alternative Route. (±)-2-(5-Methoxy-2,3-dihydrobenzofuran-3-yl)ethyl *p*-Toluenesulfonate ((±)-17).** A solution of $Et_3N$ (170 mL, 1.22 mol) in $CH_2Cl_2$ (400 mL) was added dropwise to a 0 °C solution of alcohol (±)-**16** (78.6 g, 405 mmol) and *p*-toluenesulfonyl chloride (163 g, 855 mmol) in $CH_2Cl_2$ (1300 mL). After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and stirred an additional 2 h. The reaction was then quenched by the addition of saturated $Na_2CO_3$ solution (500 mL). The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 350 mL). The organic phases were pooled and washed with saturated $Na_2CO_3$ (200 mL), dried ($MgSO_4$), filtered, and evaporated to leave a white solid that was recrystallized from EtOAc to afford white crystals (117 g, 83%): mp 88−89 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.96 (m, 1 H, $ArCHCH_2CH_2$), 2.08 (m, 1 H, $ArCHCH_2CH_2$), 2.46 (s, 3 H, $ArCH_3$), 3.50 (m, 1 H, ArC*H*), 3.75 (s, 3 H, $ArOCH_3$), 4.12 (m, 3 H, $ArCHCH_2CH_2$, $ArCHCH_2O$), 4.52 (t, 1 H, $ArCHCH_2O$, $J$ = 9.0 Hz), 6.67 (m, 3 H, Ar*H*), 7.36 (d, 2 H, Ar*H*, $J$ = 9.0 Hz), 7.81 (d, 2 H, ArH, $J$ = 6.0 Hz); MS (CI) *m*/*z* 349 (M + H). Anal. ($C_{18}H_{20}O_5S$) C, H.

**Continuation of Alternative Route. (±)-3-(5-Methoxy-2,3-dihydrobenzofuran-3-yl)propionitrile ((±)-18).** Potassium cyanide (16.0 g, 246 mmol) was added to a solution of tosylate (±)-**17** (58.8 g, 169 mmol) in absolute EtOH (1.0 L). The mixture was heated at reflux for 9 h and then cooled to room temperature. The solids were removed by vacuum filtration, and the filter cake was washed well with EtOH. The filtrate volume was reduced under vacuum (ca. 400 mL) and was then diluted with $Et_2O$ (500 mL). This solution was then washed with $H_2O$ (500 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and evaporated to leave a tan oil that was homogeneous by TLC (33 g, 97%). An analytical sample was purified by column chromatography (4:1 hexanes/EtOAc). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.98 (m, 1 H, $ArCHCH_2CH_2$), 2.07 (m, 1 H, $ArCHCH_2CH_2$), 2.41 (m, 2 H, $ArCHCH_2CH_2$), 3.55 (m, 1 H, ArC*H*), 3.77 (s, 3 H, $ArOCH_3$), 4.25 (m, 1 H, $ArCHCH_2O$), 4.63 (dt, 1 H, $ArCHCH_2O$, $J$ = 8.9, 2.6 Hz), 6.72 (m, 3 H, Ar*H*); MS (CI) *m*/*z* 204 (M + H). Anal. ($C_{12}H_{13}NO_2$) C, H, N.

**Continuation of Alternative Route. (±)-3-(5-Methoxy-2,3-dihydrobenzofuran-3-yl)propionic Acid ((±)-15).** Nitrile (±)-**18** (36.5 g, 180 mmol) was dissolved in EtOH (1.0 L), and then 2 N NaOH (500 mL) was added. The reaction mixture was heated at reflux overnight and then cooled to room temperature. The EtOH was removed by rotary evaporation, and the resulting suspension was cooled and acidified by dropwise addition of 2 N HCl. The mixture was extracted with $CH_2Cl_2$ (4 × 400 mL). The organic layers were pooled and washed with brine (300 mL), dried ($Na_2SO_4$), filtered, and evaporated to leave a white solid. Recrystallization from EtOAc gave off-white needles (33 g, 83%). NMR spectral data and the melting point were identical to those reported above.

**(±)-6-Methoxy-2,2a,3,4-tetrahydronaphtho[1,8-*bc*]furan-5-one ((±)-19).** Propionic acid (±)-**15** (33.0 g, 150 mmol) was dissolved in anhydrous benzene (850 mL), and then DMF (4 mL) was added. Oxalyl chloride (26 mL, 298 mmol) was added dropwise to the mixture, and the reaction mixture was stirred at room temperature for 4 h. The solvent and excess oxalyl chloride were removed by rotary evaporation, and the residue was dissolved in $CH_2Cl_2$ (460 mL). The reaction flask was submerged in an ice bath, and then anhydrous $SnCl_4$ (22 mL, 188 mmol) was added dropwise. The ice bath was removed, and the reaction mixture was stirred for 1 h and then poured onto ice (ca. 300 g). The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 250 mL). The organic layers were then pooled and washed with brine (200 mL), dried ($MgSO_4$), filtered, and evaporated to leave a tan solid that was recrystallized from EtOAc (29.7 g, 97%): mp 105−106 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.89 (dq, 1 H, $ArCHCH_2CH_2$, $J$ = 7.0, 2.0 Hz), 2.31 (m, 1 H, $ArCHCH_2CH_2$), 2.57 (m, 1 H, $ArCHCH_2CH_2$), 2.76 (m, 1 H, $ArCHCH_2CH_2$), 3.68 (m, 1 H, ArC*H*), 3.88 (s, 3 H, $ArOCH_3$), 4.10 (dd, 1 H, $ArCHCH_2O$, $J$ = 6.4, 4.5 Hz), 4.84 (t, 1 H, $ArCHCH_2O$, $J$ = 8.5 Hz), 6.69 (d, 1 H, Ar*H*, $J$ = 3.6 Hz), 6.93 (d, 1 H, Ar*H*, $J$ = 3.6 Hz); MS (CI) *m*/*z* 205 (M + H). Anal. ($C_{12}H_{12}O_3$) C, H.

**(±)-5-Aminomethyl-6-methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-5-ol Hydrochloride ((±)-20).** Zinc iodide (0.4 g, 1.3 mmol) was added to a solution of ketone (±)-**19** (10.0 g, 49 mmol) in $CH_2Cl_2$ (500 mL). TMSCN (7.2 mL, 54 mmol) was then added, and the reaction mixture was heated at reflux for 14 h. Comparison of the IR spectrum of the reaction mixture to the IR spectrum of the starting material

(±)-**19** indicated the absence of the C═O peak at 1681 $cm^{-1}$ and the appearance of a new peak at 2361 $cm^{-1}$ (CN). The reaction mixture was then concentrated by rotary evaporation, and the remaining residue was dissolved in anhydrous THF (200 mL) and added dropwise to a suspension of $LiAlH_4$ (2.8 g, 74 mmol) in anhydrous $Et_2O$ (100 mL). The reaction mixture was stirred overnight, and then the reaction was quenched by the *careful addition* of $H_2O$ (10 mL) dissolved in THF (100 mL). The resulting suspension was then filtered, and the filter cake was washed well with warm THF (500 mL). The filtrate was then diluted with $Et_2O$ (300 mL) and washed with $H_2O$ (2 × 200 mL), dried ($Na_2SO_4$), filtered, and evaporated to leave a tan solid. This solid was dissolved in anhydrous $Et_2O$ (200 mL) and acidified with anhydrous 1 N HCl in EtOH. The solvents were then removed by rotary evaporation and the resulting white solid was recrystallized from EtOH to afford white crystals (11.5 g, 87%): mp 191−193 °C (dec); $^1H$ NMR (500 MHz, DMSO-$d_6$) δ 1.56 (q, 1 H, ArCHC$H_2$CH$_2$, $J$ = 12.4 Hz), 1.78 (t, 1 H, ArCHC$H_2$CH$_2$, $J$ = 13.2 Hz), 1.96 (m, 1 H, ArCHCH$_2$C$H_2$, $J$ = 5.2 Hz), 2.31 (d, 1 H, ArCHCH$_2$C$H_2$, $J$ = 13.0 Hz), 2.86 (d, 1 H, C$H_2$N, $J$ = 12.9 Hz), 3.24 (d, 1 H, C$H_2$N, $J$ = 13.1 Hz), 3.26 (m, 1 H, ArC$H$, obscured in DMSO spectrum, present in $D_2O$ spectrum), 3.73 (s, 3 H, ArOC$H_3$), 3.86 (dd, 1 H, ArCHC$H_2$O, $J$ = 12.1, 4.3 Hz), 4.67 (t, 1 H, ArCHC$H_2$O, 8.3 Hz), 6.68 (dd, 2 H, Ar$H$, 9.1, 8.5 Hz), 7.89 (bs, 2 H, CH$_2$N$H_2$); MS (CI) $m/z$ 236 (M + H), 218 (M + H − $H_2O$).

**(±)-(6-Methoxy-2a,3-dihydro-2*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane Hydrochloride ((±)-21).** Concentrated HCl (40 mL) was added to a solution of the hydrochloride salt of amino alcohol (±)-**20** (18 g, 67 mmol) in absolute EtOH (500 mL). The solution was heated at reflux for 6 h, at which time it had taken on a green color. The reaction mixture was concentrated to dryness, and the resulting white solid was recrystallized from EtOH to afford white crystals (12 g, 71%): mp 255−257 °C (dec); $^1H$ NMR (500 MHz, $D_2O$) δ 1.98 (t, 1 H, ArCHC$H_2$CH, $J$ = 12.3 Hz), 2.48 (dt, 1 H, ArCHC$H_2$CH, $J$ = 16.5, 7.5 Hz), 3.44 (m, 1 H, ArC$H$CH$_2$O), 3.69 (s, 3 H, ArOC$H_3$), 3.75 (d, 1 H, C$H_2$N, $J$ = 13.2 Hz), 4.04 (d, 1 H, C$H_2$N, $J$ = 13.0 Hz), 4.06 (m, 1 H, ArCHC$H_2$O), 4.77 (t, 1 H, ArCHC$H_2$O, $J$ = 8.7 Hz), 6.04 (d, 1 H, ArCC$H$CH$_2$, $J$ = 4.2 Hz), 6.62 (d, 1 H, Ar$H$, $J$ = 5.7 Hz), 6.70 (d, 1 H, Ar$H$, $J$ = 9.0 Hz); MS (CI) $m/z$ 218 (M + H), 201 (M + H − $NH_3$). Anal. ($C_{13}H_{16}ClNO_2$) C, H, N.

**(±)-*syn*-(6-Methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane Hydrochloride ((±)-4a).** The hydrochloride salt of aminostyrene (±)-**21** (7.0 g, 28 mmol) was dissolved in a mixture of MeOH (175 mL) and EtOH (50 mL) and added to a Parr hydrogenation flask containing 10% Pd/C (0.70 g) and EtOH (10 mL). The flask was placed on a hydrogenation apparatus, pressurized to 60 psi of $H_2$, and shaken for 24 h. The reaction mixture was then vacuum-filtered through a pad of Celite, and the filter cake was washed well with MeOH. The solvents were removed by rotary evaporation, and the resulting white solid was recrystallized from EtOH (7.0 g, 99%): mp 262−263 °C; $^1H$ NMR (500 MHz, $D_2O$) δ 1.34 (q, 1 H, ArCHC(3)$H_2$CH$_2$, $J$ = 12.3 Hz), 1.87 (dt, 1 H, ArCHC(3)$H_2$CH$_2$, $J$ = 11.7, 5.5 Hz), 2.00 (t, 2 H, ArCHCH$_2$C(4)$H_2$, $J$ = 14.6 Hz), 2.90 (dd, 1 H, ArC$H$CH$_2$N, $J$ = 12.6, 4.2 Hz), 3.17 (dd, 1 H, C$H_2$N, $J$ = 12.6, 4.8 Hz), 3.22 (m, 2 H, C$H_2$N, ArC$H$CH$_2$O), 3.75 (s, 3 H, ArOC$H_3$), 3.91 (dd, 1 H, ArCHC$H_2$O, 12.8, 8.2 Hz), 4.71 (t, 1 H, ArCHC$H_2$O, $J$ = 8.2 Hz, obscured in $D_2O$ spectrum, present in DMSO spectrum), 6.64 (d, 1 H, Ar$H$, $J$ = 8.5 Hz), 6.70 (d, 1 H, Ar$H$, $J$ = 8.5 Hz); MS (CI) $m/z$ 220 (M + H), 203 (M + H − $NH_3$). Anal. ($C_{13}H_{18}ClNO_2$) C, H, N.

**(±)-*syn*-(8-Bromo-6-methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane Hydrochloride ((±)-4b).** Bromine (0.80 g, 5.0 mmol, 0.2 N MeOH solution) was added dropwise to a solution of (±)-**4a** (1.28 g, 5.0 mmol) in MeOH (150 mL) at 0 °C. The yellow solution turned clear upon warming to room temperature. $Et_2O$ (200 mL) was added, and the precipitate that formed was collected by vacuum filtration. This solid was stirred in concentrated $NH_4OH$ solution (300 mL) and extracted with $CH_2Cl_2$ (4 × 100 mL). The organic phases were pooled, dried ($Na_2SO_4$), filtered, and evaporated to leave a clear oil. The resulting oil was dissolved in anhydrous $Et_2O$, filtered through a small plug of glass wool, and acidified with 1 N ethanolic HCl. The precipitate was collected by vacuum filtration and then recrystallized from *i*-PrOH to yield needle-like crystals (1.5 g, 88%): mp 258−260 °C (dec); $^1H$ NMR (500 MHz, $D_2O$) δ 1.38 (q, 1 H, ArCHC(3)$H_2$CH$_2$, $J$ = 12.2 Hz), 1.84 (m, 1 H, ArCHC(3)$H_2$CH$_2$), 2.04 (m, 2 H, ArCHCH$_2$C(4)$H_2$), 2.92 (dt, 1 H, ArC$H$CH$_2$N, $J$ = 10.2, 3.6 Hz), 3.18 (d, 2 H, C$H_2$N, $J$ = 8.8 Hz), 3.32 (m, 1 H, ArC$H$CH$_2$O), 3.78 (s, 3 H, ArOC$H_3$), 4.01 (dd, 1 H, ArCHC$H_2$O, $J$ = 12.7, 8.7 Hz), 4.84 (t, 1 H, ArCHC$H_2$O, $J$ = 8.3 Hz), 6.89 (s, 1 H, Ar$H$); MS (CI) $m/z$ 298 (M + H), 300. Anal. ($C_{13}H_{17}BrClNO_2$) C, H, N.

**(±)-*syn*-*N*-Trifluoroacetyl-1-(8-bromo-6-methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane ((±)-22).** To a stirred suspension of the hydrobromide salt of (±)-**4b** (1.3 g, 3.6 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.04 g, 0.3 mmol) in $CH_2Cl_2$ (40 mL) was added $Et_3N$ (16.0 mL, 12.0 mmol), and the mixture was cooled to 0 °C. Trifluoroacetic anhydride (2.5 mL, 17 mmol) was then added to the reaction dropwise. The mixture was allowed to warm to room temperature and stirred for 8 h. The mixture was then diluted with $CH_2Cl_2$ (50 mL) and washed with 2 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic phase was then dried ($MgSO_4$), filtered, and evaporated to leave a white solid that was recrystallized from $Et_2O$ (1.2 g, 92%): mp 197−198 °C; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.55 (q, 1 H, ArCHC(3)$H_2$CH$_2$, $J$ = 11.4 Hz), 1.86 (dt, 1 H, ArCHC(3)$H_2$CH$_2$, $J$ = 13.1, 5.8 Hz), 2.02 (d, 2 H, ArCHCH$_2$C(4)$H_2$, $J$ = 11.6 Hz), 3.16 (q, 1 H, ArC$H$CH$_2$N, $J$ = 6.3 Hz), 3.38 (m, 1 H, ArCHC$H_2$N), 3.42 (m, 1 H, ArCHC$H_2$N), 3.53 (p, 1 H, ArC$H$CH$_2$O, $J$ = 6.7 Hz), 3.81 (s, 3 H, ArOCH$_3$), 4.06 (dd, 1 H, ArCHC$H_2$O, $J$ = 13.0, 8.3 Hz), 4.81 (t, 1 H, ArCHC$H_2$O, $J$ = 8.2 Hz), 6.72 (s, 1 H, Ar$H$), 7.26 (bs, 1 H, N$H$COCF$_3$); MS (CI) $m/z$ 394 (M + H), 396. Anal. ($C_{15}H_{15}BrF_3NO_3$) C, H, N.

**(±)-*N*-Trifluoroacetyl-1-(8-bromo-6-methoxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane ((±)-23).** A solution of DDQ (1.73 g, 7.6 mmol) in dioxane (250 mL) was added slowly to a solution of (±)-**22** (3.0 g, 7.6 mmol) in dioxane (100 mL). The reaction mixture was stirred at room temperature for 8 h and was then diluted with $CH_2Cl_2$ (100 mL) and filtered through a short pad of silica gel. The silica gel was washed thoroughly with $CH_2Cl_2$, and the filtrate and wash were then reduced to dryness by rotary evaporation. The black solid that resulted was subjected to column chromatography (1:1 hexanes/EtOAc as eluent), resulting in an off-white, solid product that was recrystallized from $Et_2O$ to afford white, fluffy crystals (2.3 g, 78%): mp 172−174 °C; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.92 (m, 1 H, ArCCH$_2$C$H_2$), 2.13 (dt, 1 H, ArCCH$_2$C$H_2$, $J$ = 6.2 Hz), 2.72 (m, 1 H, ArCC$H_2$CH$_2$), 2.85 (dt, 1 H, ArCC$H_2$CH$_2$, $J$ = 13.9, 2.2 Hz), 3.34 (td, 1 H, ArCHC$H_2$N, $J$ = 13.6, 3.1 Hz), 3.49 (m, 1 H, ArCHC$H_2$N), 3.64 (dt, 1 H, ArC$H$, $J$ = 12.3, 3.5 Hz), 3.91 (s, 3 H, ArOC$H_3$), 7.03 (s, 1 H, Ar$H$), 7.40 (s, 1 H, Ar$H$), 7.62 (bs, 1 H, N$H$COCF$_3$); MS (CI) $m/z$ 392 (M + H). Anal. ($C_{15}H_{13}BrF_3NO_3$) C, H, N.

**(±)-(8-Bromo-6-methoxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane Hydrochloride ((±)-6b).** A solution of (±)-**23** (1.1 g, 2.8 mmol) in MeOH (150 mL) was cooled to 0 °C, and then 5 N KOH solution (25 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred overnight, and then the MeOH was removed by rotary evaporation. The residue was diluted with $H_2O$ (25 mL) and extracted with $Et_2O$ (4 × 100 mL), dried ($Na_2SO_4$), filtered, and evaporated to afford a clear oil. This oil was dissolved in $Et_2O$ (100 mL), filtered through a plug of glass wool, and neutralized by the slow addition of 1 N ethanolic HCl. The solvents were removed by rotary evaporation and the resulting white residue was recrystallized from MeOH to afford the title compound (0.6 g, 67%): mp 222−223 °C; $^1H$ NMR (500 MHz, $CD_3OD$) δ 1.82 (m, 1 H, ArCCH$_2$C$H_2$), 2.19 (dt, 1 H, ArCCH$_2$C$H_2$, $J$ = 11.6, 2.7 Hz), 2.72 (t, 1 H, ArCC$H_2$CH$_2$, $J$ = 13.4 Hz), 2.75 (m, 1 H, ArCC$H_2$CH$_2$), 3.04 (dd, 1 H, ArCHC$H_2$N, $J$ = 13.1, 6.4 Hz), 3.10 (dd, 1 H, ArCHC$H_2$N, $J$ =

12.9, 6.4 Hz), 3.45 (m, 1 H, ArC*H*CH$_2$N), 3.83 (s, 3 H, ArOC*H*$_3$), 7.07 (s, 1 H, Ar*H*), 7.48 (s, 1 H, Ar*H*); MS (CI) *m*/*z* 296 (M + H). Anal. (C$_{13}$H$_{15}$BrClNO$_2$) C, H, N.

**(±)-*syn*-*N*-Trifluoroacetyl-(6-methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane ((±)-24).** To a stirred suspension of the hydrochloride salt of (±)-**4a** (3.1 g, 12.1 mmol) and 4-*N*,*N*-(dimethylamino)pyridine (0.12 g, 0.98 mmol) in CH$_2$Cl$_2$ (150 mL) was added Et$_3$N (6.0 mL, 43.0 mmol), and the mixture was cooled to 0 °C. Trifluoroacetic anhydride (4.13 mL, 29.0 mmol) was then added to the reaction mixture dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 8 h. The mixture was diluted with CH$_2$Cl$_2$ (200 mL) and washed with 2 N HCl (100 mL), saturated NaHCO$_3$ (100 mL), and brine (100 mL). The organic phase was then dried (MgSO$_4$), filtered, and evaporated to leave a white solid that was recrystallized from Et$_2$O (3.5 g, 91%): mp 181−183 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.51 (q, 1 H, ArCHC(3)*H*$_2$CH$_2$, *J* = 13.0 Hz), 1.88 (dt, 1 H, ArCHC(3)*H*$_2$CH$_2$, *J* = 9.6, 5.7 Hz), 2.01 (m, 2 H, ArCHCH$_2$C-(4)*H*$_2$), 3.23 (p, 1 H, ArC*H*CH$_2$N, *J* = 7.0 Hz), 3.28 (m, 1 H, ArC*H*CH$_2$O), 3.40 (m, 1 H, ArCHC*H*$_2$N), 3.57 (p, 1 H, ArCHC*H*$_2$N, *J* = 6.3 Hz), 3.82 (s, 3 H, ArOC*H*$_3$), 3.96 (dd, 1 H, ArCHC*H*$_2$O, *J* = 12.9, 8.2 Hz), 4.72 (t, 1 H, ArCHC*H*$_2$O, *J* = 8.1 Hz), 6.62 (s, 2 H, Ar*H*), 7.64 (bs, 1 H, N*H*COCF$_3$); MS (CI) *m*/*z* 316 (M + H). Anal. (C$_{15}$H$_{16}$F$_3$NO$_3$) C, H, N.

**(±)-*N*-Trifluoroacetyl-(6-methoxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane ((±)-25).** A solution of DDQ (2.16 g, 9.5 mmol) in dioxane (330 mL) was added slowly to a solution of (±)-**24** (3.0 g, 9.5 mmol) in dioxane (125 mL). The reaction mixture was stirred at room temperature for 8 h and was then diluted with CH$_2$Cl$_2$ (100 mL) and filtered through a short pad of silica gel. The silica gel was washed well with CH$_2$Cl$_2$, and the filtrate and wash were reduced to dryness by rotary evaporation. The dark solid that resulted was subjected to column chromatography (1:1 hexanes/EtOAc as eluent), resulting in a off-white, solid product that was recrystallized from Et$_2$O to afford white, fluffy crystals (2.6 g, 88%): mp 141−142 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.95 (m, 1 H, ArCCH$_2$C*H*$_2$), 2.13 (dt, 1 H, ArCCH$_2$C*H*$_2$, *J* = 13.9, 2.2 Hz), 2.73 (t, 1 H, ArCC*H*$_2$, *J* = 13.6 Hz), 2.85 (d, 1 H, ArCC*H*$_2$, *J* = 16.2 Hz), 3.37 (dt, 1 H, ArCHC*H*$_2$N, *J* = 12.3, 3.5 Hz), 3.52 (m, 1 H, ArC*H*CH$_2$N), 3.68 (m, 1 H, ArCHC*H*$_2$N), 3.92 (s, 3 H, ArOC*H*$_3$), 6.88 (d, 1 H, Ar*H*, *J* = 8.8 Hz), 7.28 (d, 1 H, Ar*H*, *J* = 8.8 Hz), 7.35 (s, 1 H, Ar*H*), 7.83 (bs, 1 H, N*H*COCF$_3$); MS (CI) *m*/*z* 314 (M + H). Anal. (C$_{15}$H$_{14}$F$_3$NO$_3$) C, H, N.

**(±)-(6-Methoxy-4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane Hemioxalate ((±)-6a).** A solution of (±)-**25** (1.7 g, 5.4 mmol) in MeOH (250 mL) was cooled to 0 °C, and then 5 N KOH solution (30 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred overnight, and then the MeOH was removed by rotary evaporation. The residue was diluted with H$_2$O (25 mL) and extracted with Et$_2$O (4 × 100 mL), dried (Na$_2$SO$_4$), filtered, and evaporated to afford a clear oil. This oil was dissolved in Et$_2$O (100 mL), filtered through a plug of glass wool, and neutralized by the slow addition of oxalic acid (54 mL, 0.1 M in MeOH). The solvents were removed, and the resulting white residue was recrystallized from MeOH to afford the hemioxalate salt (0.9 g, 59%): mp 243 °C; $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 1.82 (m, 1 H, ArCCH$_2$C*H*$_2$), 2.17 (dt, 1 H, ArCCH$_2$C*H*$_2$, *J* = 11.9, 2.8 Hz), 2.69 (t, 1 H, ArCC*H*$_2$, *J* = 13.6 Hz), 2.78 (dt, 1 H, ArCC*H*$_2$, *J* = 12.0, 3.1 Hz), 3.03 (m, 2 H, ArCHC*H*$_2$N, *J* = 13.0, 6.4 Hz), 3.46 (m, 1 H, ArC*H*CH$_2$), 3.81 (s, 3 H, ArOC*H*$_3$), 6.88 (d, 1 H, Ar*H*, *J* = 8.7 Hz), 7.19 (d, 1 H, Ar*H*, *J* = 8.7 Hz), 7.35 (s, 1 H, Ar*H*); MS (CI) *m*/*z* 218 (M + H). Anal. (C$_{15}$H$_{17}$NO$_6$) C, H, N.

**(±)-*anti*-(6-Methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho-[1,8-*bc*]furan-5-yl)aminomethane Hydrochloride ((±)-5a).** The primary amine of (±)-**6a** (0.17 g, 0.83 mmol) was dissolved in hexane (200 mL) and added to a Parr flask containing 10% Pd/C (0.10 g) and hexane (5 mL). The flask was then pressurized and shaken at 65 psi of H$_2$ for 24 h. The solution was filtered through Celite, the filter cake was washed well with EtOH, and the solvents were removed by rotary evaporation to leave a clear oil. This oil was dissolved in anhydrous Et$_2$O (100 mL) and filtered through a small plug of glass wool. The solution was then acidified with ethanolic 1 N HCl and the precipitate that formed was collected by vacuum filtration and then recrystallized from *i*-PrOH to afford needle-like crystals (0.14 g, 81%): mp 185−186 °C; $^1$H NMR (500 MHz, D$_2$O) $\delta$ 1.22 (q, 1 H, ArCHC(3)*H*$_2$CH$_2$, *J* = 11.2 Hz), 1.52 (q, 1 H, ArCHC(3)*H*$_2$CH$_2$, *J* = 9.7 Hz), 2.18 (dd, 1 H, ArCHCH$_2$C(4)*H*$_2$, *J* = 12.5, 3.3 Hz), 2.30 (d, 1 H, ArCHCH$_2$C-(4)*H*$_2$, *J* = 12.2 Hz), 3.30 (dd, 2 H, C*H*$_2$N, *J* = 12.4, 7.6 Hz), 3.34 (m, 1 H, ArC*H*CH$_2$O), 3.38 (m, 1 H, ArC*H*CH$_2$N), 3.78 (s, 3 H, ArOC*H*$_3$), 3.97 (t, 1 H, ArCHC*H*$_2$O, *J* = 10.4 Hz), 4.84 (t, 1 H, ArCHC*H*$_2$O, *J* = 8.4 Hz), 6.71 (d, 1 H, Ar*H*, *J* = 8.3 Hz), 6.77 (d, 1 H, Ar*H*, *J* = 8.5 Hz); MS (CI) *m*/*z* 220 (M + H), 203 (M + H − NH$_3$). Anal. (C$_{13}$H$_{18}$ClNO$_2$) C, H, N.

**(±)-*anti*-(8-Bromo-6-methoxy-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]furan-5-yl)aminomethane Hydrochloride ((±)-5b).** Bromine (0.16 g, 1.0 mmol, 0.2 N MeOH solution) was added dropwise to a solution of the hydrochloride salt of (±)-**5a** (0.26 g, 1.0 mmol) in MeOH (25 mL) at 0 °C. The reaction mixture was stirred and allowed to warm to room temperature overnight. Et$_2$O (75 mL) was added, and the precipitate that formed was collected by vacuum filtration. This solid was stirred in concentrated NH$_4$OH solution (100 mL) and extracted with Et$_2$O (4 × 100 mL). The organic phases were pooled and dried (Na$_2$SO$_4$), filtered, and evaporated to leave a clear oil. This oil was dissolved in anhydrous Et$_2$O, filtered through a small plug of glass wool, and acidified with 1 N ethanolic HCl. The precipitate was collected by vacuum filtration and then recrystallized from *i*-PrOH to yield needle-like crystals (0.26 g, 78%): mp 231−232 °C; $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 1.25 (1 H, q, ArCHC(3)*H*$_2$CH$_2$, *J* = 12.1 Hz), 1.53 (1 H, m, ArCHC(3)*H*$_2$CH$_2$), 2.18 (1 H, dd, ArCHCH$_2$C(4)-*H*$_2$, *J* = 12.3, 3.8 Hz), 2.25 (1 H, m, ArCHCH$_2$C(4)*H*$_2$), 3.16 (1 H, m, C*H*$_2$N), 3.37 (1 H, m, C*H*$_2$N), 3.43 (1 H, m, ArC*H*CH$_2$N), 3.76 (3 H, s, ArOC*H*$_3$), 3.96 (1 H, t, ArCHC*H*$_2$O, *J* = 8.8 Hz), 4.75 (1 H, t, ArCHC*H*$_2$O, *J* = 7.9 Hz), 6.80 (1 H, s, Ar*H*); MS (CI) *m*/*z* 298 (M + H). Anal. (C$_{13}$H$_{17}$BrClNO$_2$) C, H, N.

**Pharmacology Methods: Cell Culture.** Cells stably transfected to express the rat 5-HT$_{2A}$, rat 5-HT$_{2C}$, or human 5-HT$_{1A}$ receptor were maintained in Dulbecco's minimum essential medium, containing 10% dialyzed fetal bovine serum (Gibco BRL) and supplemented with L-glutamine, Pen/Strep, and Geneticin.[26] The cells were cultured at 37 °C in a H$_2$O saturated atmosphere of 95% air and 5% CO$_2$. For radioligand binding assays, cells were split into 100 mm culture dishes when they reached 90% confluency. Upon reaching 100% confluency in the culture dishes, the cells were washed with sterile filtered phosphate-buffered solution and left to incubate in serum-free Opti-MEM for 5 h. After incubation, the cells were harvested by centrifugation (15000*g*, 20 min) and placed immediately in a freezer at −80 °C until the assay was performed. For IP$_3$ accumulation experiments, the cells were seeded into 24-well plates and assays were performed when 70% confluency was achieved.

**Radioreceptor Competition Assays.** For saturation assays, 0.125−5.0 nM [$^{125}$I]-DOI was used for the 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors and 0.25−10 nM [$^3$H]-8-OH-DPAT was used for the 5-HT$_{1A}$ receptor. The total volume of the assay was 250 $\mu$L. Nonspecific binding was defined in the presence of 10 $\mu$M cinanserin (rat 5-HT$_{2A}$ receptor expressing cells), 10 $\mu$M mianserin (rat 5-HT$_{2C}$ receptor expressing cells), or 10 $\mu$M 5-HT (human 5-HT$_{1A}$ receptor expressing cells). Competition binding experiments were carried out in a total volume of 500 $\mu$L with 0.20 nM [$^{125}$I]-DOI or 2.0 nM [$^3$H]-8-OH-DPAT. Previously harvested cells were resuspended and added to each well containing assay buffer (50 mM Tris, 0.1 mM EDTA, 10 mM MgCl$_2$; pH 7.4), radioligand, and test compound (or in the case of the saturation assays, cinanserin, mianserin, or 5-HT). Incubation was carried out at 25 °C for 60 min and terminated by rapid filtration using a prechilled Packard 96-well harvester with GF/B Uni-filters that had been preincubated for 30 min in 0.3% polyethylenimine. The filters were rinsed using chilled wash buffer (10 mM Tris, 154 mM NaCl) and left to dry

overnight. The following day, Microscint-O was added and radioactivity was determined using a TopCount (Packard) scintillation counter. GraphPad Prism (GraphPad Software, San Diego, CA) was used to analyze the saturation and competition binding curves.

**Inositol Triphosphate Accumulation Studies in Cells Expressing the 5-HT$_{2A}$ Receptor.** Accumulation of inositol phosphates was determined using a modified version of a previously published protocol.[27] Briefly, cells expressing the rat 5-HT$_{2A}$ receptor were labeled for 18−20 h in CRML medium containing 1.0 $\mu$Ci/mL [$^3$H]-myo-inositol. After pretreatment of the cells with 10 $\mu$M pargyline/10 mM LiCl for 15 min, the cells were exposed to a test drug for 30 min at 37 °C under an atmosphere of 95% $O_2$ and 5% $CO_2$. The assay was terminated by aspirating the medium and adding 10 mM formic acid. Following incubation for 16 h at 4 °C, the [$^3$H]-inositol phosphates were separated from the cellular debris on Dowex-1 ion-exchange columns and eluted with 1.0 M ammonium formate and 0.10 M formic acid. The vials were counted for tritium using a TriCarb scintillation counter (Packard Instrument Corp.).

**Drug Discrimination Studies.** Male Sprague−Dawley rats (Harlan Laboratories, Indianapolis, IN) weighing 200−220 g at the beginning of the drug discrimination study were divided into six groups ($n$ = 8−15 per group) and trained to discriminate LSD tartrate or DOI hydrochloride from saline. None of the rats had previously received drugs or behavioral training. Water was freely available in the individual home cages, and a rationed amount of supplemental feed (Purina Lab Blox) was made available after experimental sessions to maintain approximately 80% of free-feeding weight.

Six standard experimental chambers (model E10-10RF, Coulbourn Instruments, Lehigh Valley, PA) consisted of modular test cages enclosed within sound-attenuated cubicles with fans for ventilation and background white noise. A white house light was centered near the top of the front panel of the cage, which was also equipped with two response levers separated by a food hopper, all positioned 2.5 cm above the floor.

A fixed ratio (FR) 50 schedule of food reinforcement (Noyes 45 mg of dustless pellets) in a two-lever paradigm was used. The complete drug discrimination procedure has been described in detail elsewhere.[28]

**Acknowledgment.** We thank Stewart Frescas and Amjad Qandil for their helpful contributions and discussions pertaining to this work. We also thank for their kind donations Dr. David Julius (UCSF) for the 5-HT$_{2A}$ and 5-HT$_{2C}$ cell lines as well as Dr. Christopher Harber (Pharmacia) for the 5-HT$_{1A}$ cell line. This work was supported by Grant DA02189 from NIDA and by a grant from the Heffter Research Institute.

**Supporting Information Available:** X-ray crystallographic information for (±)-**4a** and (±)-**5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM030064V